Clinical, Epidemiological, and Molecular study of Holoprosencephaly in France

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Holoprosencephaly (HPE ; 1/16.000 live births ; 1/250 conceptuses) is a common developmental defect that involves both the forebrain and the face. Clinical expressivity is variable, ranging from a single cerebral ventricle and cyclopia to clinically symptom-free obligated carriers in familial HPE. The disease is genetically heterogeneous but additional environmental agents also participate in its etiology.

In 1996, before the identification of HPE genes, we conducted an epidemiological study[1] from 258 HPE records with a segregation analysis involving 79 families with nonsyndromic and nonchromosomal HPE. The proportion of sporadic cases was estimated 68% and the prediction of the recurrent risk after an isolated case 14%.

Our study now includes 126 unrelated nonchromosomal HPE cases (76 typical HPE, 25 atypical cases, 25 polymalformative cases). We provide clinical data regarding the subgroup of typical HPE. 35% were familial cases. Other brain malformations were associated with HPE in 23 cases, especially hypoplastic cerebellar vermis (10) and neural tube defects (9). We report 21 novel heterozygous mutations (16% of all cases, 25% of typical HPE cases), 12 in *Sonic hedgehog* gene (*SHH*)[3], 5 in *ZIC2*[5], 3 in *SIX3*[4], and 1 in *TGIF*. Ten mutations were found in familial cases whereas 11 mutations were identified in apparently sporadic cases. Original phenotypes associated with a mutation have been noticed: isolated cleft lip and palate, abnormalities of the pituitary gland and the corpus callosum, colobomatous microphthalmia and brachymetacarpia, choanal stenosis, without HPE. This study confirms the great diversity of phenotypes in HPE families and the genetic heterogeneity of the disease.

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